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fMRI characterisation of widespread brain networks relevant for behavioural variability in fine hand motor control with and without visual feedback

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ABSTRACT

A bilateral visuo-parietal-motor network is responsible for fine control of hand movements. However, the sub-regions which are devoted to maintenance of contraction stability and how these processes fluctuate with trial-quality of task execution and in the presence/absence of visual feedback remains unclear. We addressed this by integrating behavioural and fMRI measurements during right-hand isometric compression of a compliant rubber bulb, at 10% and 30% of maximum voluntary contraction, both with and without visual feedback of the applied force. We quantified single-trial behavioural performance during 1) the whole task period and 2) stable contraction maintenance, and regressed these metrics against the fMRI data to identify the brain activity most relevant to trial-by-trial fluctuations in performance during specific task phases. fMRI-behaviour correlations in a bilateral network of visual, premotor, primary motor, parietal and inferior frontal cortical regions emerged during performance of the entire feedback task, but only in premotor, parietal cortex and thalamus during the stable contraction period. The trials with the best task performance showed increased bilaterality and amplitude of fMRI responses. With feedback, stronger BOLD-behaviour coupling was found during 10% compared to 30% contractions. Only a small subset of regions in this network were weakly correlated with behaviour without feedback, despite wider network activated during this task than in the presence of feedback. These findings reflect a more focused network strongly coupled to behavioural fluctuations when providing visual feedback, whereas without it the task recruited widespread brain activity almost uncoupled from behavioural performance.

Introduction

The fine control and smooth execution of precision grasping is essential for dexterous manipulation of objects and many actions in everyday life. The successful performance of such an action requires co-ordination of complex components including tactile and cutaneous sensory feedback, grip force control, visual cues and internal representations in order to control the magnitude, rate, direction and duration of applied force at the object surface. The organization of the brain's activity during the coordination of precision or force gripping, using either dynamic or isometric contractions, has been investigated by numerous functional magnetic resonance imaging (fMRI) studies as a foundation for studying more complex motor tasks (Binkofski et al., 2000; Castiello, 2005; Castiello and Begliomini, 2008; Debaere et al., 2003; Ehrsson et al., 2000; Ehrsson et al., 2001; Grol et al., 2007; Haller et al., 2009; Holmstrom et al., 2011; Keisker et al., 2010; Kuhtz-Buschbeck et al., 2001; Pope et al., 2005; Vaillancourt et al., 2003). This body of work has identified a bilateral fronto-parieto-cerebellar network, primarily comprised of primary sensorimotor cortex (M1/S1), dorsal and ventral premotor cortices (PMd and PMv), supplementary and cingulate motor areas (SMA and CMA), prefrontal cortex, parietal association cortex and the cerebellum.

Further work has shown the sub-components of this network which are responsible for force generation and reported that the relationship between increasing force output and amplitude of the fMRI response is linear in M1, at least up to 80% maximum voluntary contraction (MVC) (Dai et al., 2001), but more complex in other areas of the network (Cramer et al., 2002; Dai et al., 2001; Dettmers et al., 1995; Ehrsson et al., 2001; Keisker et al., 2009; Kuhtz-Buschbeck et al., 2008; Peck et al., 2001). This suggests that visual input, attention, and muscle

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recruitment also modulate the BOLD signal during a visuomotor task. To further understand control of grip tasks, fMRI studies have compared activated brain regions between precision grip tasks that are performed using thumb and forefingers and power grip tasks which use the whole hand (Ehrsson et al., 2000; Kuhtz-Buschbeck et al., 2008), as well as between static and dynamic isometric contractions (Keisker et al., 2010; Neely et al., 2013a; Thickbroom et al., 1999). This body of work supports our understanding of the differential contribution of the various regions of the visuo-sensorimotor network in the production and control of fine-graded grip forces.

It is widely recognized that continuous sensory feedback plays a crucial role in accurate motor control in everyday life. Feedback information is used to adapt force output and to correct errors (Jenmalm et al., 2006; Johansson and Westling, 1988). An optimized, feedback loop integrates visual information into the motor commands which link the primary motor cortex activity to the limb physics subtending motor behaviour (Scott, 2004). Such transformations are mediated by the dominant, dorsal-stream, visuo-motor pathway (Goodale and Milner, 1992; Johnson et al., 1996), which is distinct from the pathways of somatosensory proprioception (Lam and Pearson, 2002; Squire et al., 2003). fMRI studies have investigated the cortical basis of visual feedback control of movement by comparing the networks involved between when feedback is and is not available although it remains unclear to what extent external (visual feedback) and internal (no visual feedback) modes of motor control may arise from distinct brain networks in young, healthy adults. The lateral visual cortex, the cerebellum, inferior parietal cortex, intra parietal sulcus and lateral premotor cortex dominate during externally guided movements, whereas cingulate cortex, frontal operculum and basal ganglia activation are prominent during internally guided movements along with regions such as the primary motor cortex, supplementary motor area (SMA) secondary somatosensory areas (S2) which are recruited by both modes (Debaere et al., 2003; Heuninckx et al., 2010; Jenkins et al., 2000; Jueptner and Weiller, 1995; Kawashima et al., 2000; Kuhtz-Buschbeck et al., 2008; Rao et al., 1997; Vaillancourt et al., 2003).

However, the majority of our current knowledge concerning the brain regions recruited by motor tasks comes from fMRI analyses that assume the brain activation is consistent across repeated task executions. Such an analysis approach neglects the fact that motor control tasks demonstrate considerable intrinsic, between-trial variability in components such as response speed and the magnitude, duration, accuracy and stability of contraction force which all contribute to variations in the quality of overall task performance. Previous work has shown that human movements exhibit considerable trial-by-trial variability which has been largely attributed to noise that corrupts motor commands (van Beers et al., 2004). Studies in other sensory modalities have shown that trial-by-trial response variability contains perceptually relevant information regarding the temporal dynamics of network activity (Debener et al., 2005; Eichele et al., 2005; Mayhew et al., 2013; Scaglione et al., 2011; Scheibe et al., 2010). Therefore in the current study we adopt a similar approach, combining quantification of task performance with single-trial fMRI analysis to better understand the manner in which sub-regions of these networks preferentially support different response components of motor control and how modulations in the activity in these brain regions is related to the trial-by-trial variability in the quality of task execution. Obtaining an improved understanding of the functional role of specific brain processes that support motor task performance in the healthy brain prospectively helps form a better understanding of motor control strategies implemented in disease pathology or ageing (Heuninckx et al., 2010; Neely et al., 2013b; Prodoehl et al., 2013; Ward et al., 2008) and is important for improving brain machine interfaces and therapeutic intervention to support motor recovery in diverse neurological diseases.

Here, we used fMRI to investigate the brain regions whose activity is most important for the performance of a unilateral precision grip task. Subjects performed a right-hand isometric contraction against the resistance of a semi-compliant, rubber bulb either with or without visual feedback at two levels of contraction force (30% and 10% of the maximal voluntary contraction – MVC). These force levels were chosen as conditions where the linearity between force output and amplitude of the fMRI in motor cortex was preserved, and also where fine motor control was required for accurate task performance, rather than high force production. Using a single-trial quantification of behavioural performance derived from recorded contraction force time series, we investigate the brain areas where the fMRI response amplitude covaried with task performance on a trial-by-trial basis. We aim to identify differential brain activity between force levels, and between visually-informed motor contractions and contractions performed without visual feedback. Furthermore we further aim to dissociate the brain regions responsible for the steady maintenance of contraction force from those associated with the full task execution which included visuo-motor reaction time as well as reaching and maintaining the desired force level.

We hypothesize that fluctuations in brain activity in the visuo-parietal-motor network will be positively correlated with the quality of behavioural performance, and most strongly coupled during the visual feedback compared to the no feedback task due to the continual adaptation this task requires. By exploiting information contained in behavioural performance variability, with and without feedback, we shed further light on the integration of visual information into motor control of precision grip tasks.

Materials and methods

Experimental paradigm

Written informed consent was obtained from all participants and the protocol was approved by the Research Ethics Board of the University of Birmingham.

Seventeen right-handed subjects (age=26 ± 4 years, 7 females) performed an isometric contraction of a pneumatic rubber bulb (van Wijk et al., 2009) opposing the thumb to the first two fingers of their right-hand. Handedness of every subject was assessed using the Edinburgh handedness inventory, group mean ± standard deviation=91.8 ± 14.1. Individual's maximal voluntary contraction (MVC) of this grip was measured prior to the experiment using a mechanical hand dynamometer (0–100 kgs, Lafayette 78010, Indiana). Three trials were performed where subject's held maximum contraction for 5 s and the mean force value across trials was used as their MVC. The pneumatic device enabled the accurate measurement of contraction force, thus enabling task performance to be quantified. An increase in the contraction force applied to the rubber bulb increased the pneumatic pressure inside a rubber tube, which was translated into an analogue electrical signal by in-house electronics and recorded by a Ni-DAQ (National Instruments) (van Wijk et al., 2009). Prior to the experiments, the pneumatic equipment was calibrated so that the conversion of applied force to current was known. The contraction force was continuously recorded throughout all experiments at 100 Hz sampling rate.

During the experiment, subjects were instructed to maintain the isometric contraction for the 5-second trial duration at one of two force levels: either 10% or 30% of MVC. Throughout the experiment subjects viewed a visual display, which was projected onto a screen situated behind them at the rear of the scanner bore, via a mirror mounted on the MRI headcoil. Subjects kept their eyes open at all times and maintained fixation upon a vertical, white force-gauge that was centrally displayed upon a grey background throughout. The position of two segments aside the gauge indicated the required force (either 10% or 30% of MVC), and their appearance communicated the onset of each trial (Fig. 1). Subjects were instructed to smoothly increase the contraction force and to then maintain this target force level as

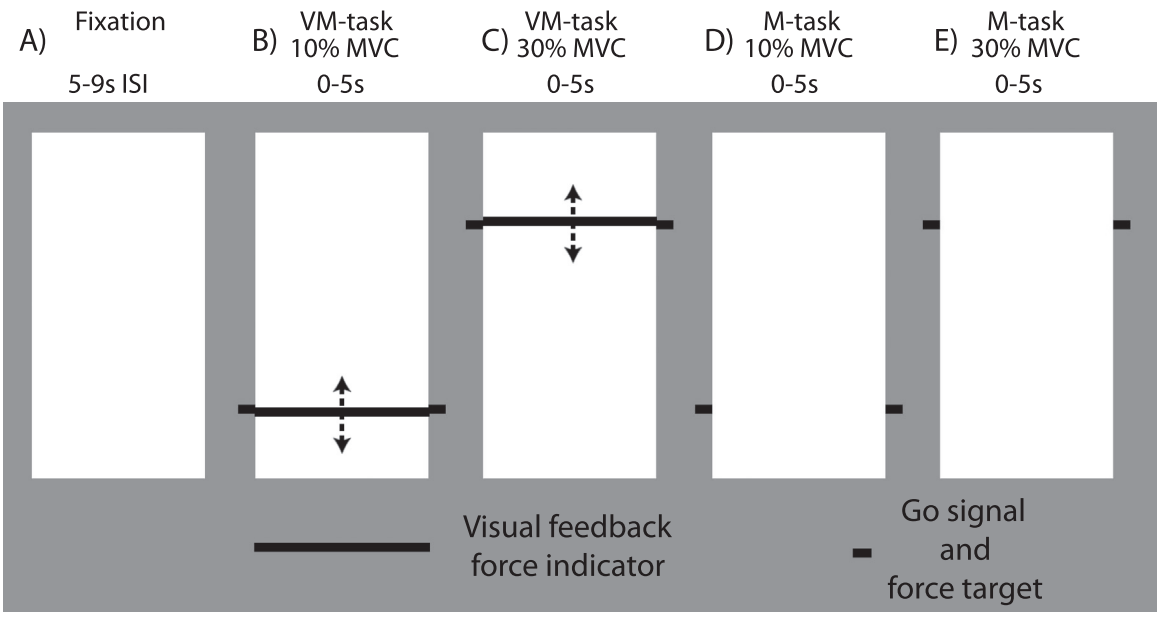

Fig. 1. Experimental conditions. Illustration of the visual display during the four task conditions. A rectangular white force gauge was displayed throughout all runs of the experiment and served as the resting fixation condition (A) during the 5, 7 or 9 s inter-stimulus interval. The visual display during the whole 5 s duration of the visuomotor feedback (VM) task 10% (B) and 30% (C) contractions; and motor (M) task 10% (D) and 30% (E) contractions are also shown. The trial onset GO signal was provided by the appearance of the two black side-bars instructing the target force level required in each trial. In the VM-task only, a horizontal black bar indicating the current contraction force was also displayed from trial onset. This force indicator bar moved vertically up/down the screen when the subject exerted greater/lesser force to provide real-time visual feedback of task performance. The movement of the indicator bar is illustrated in the figure using dashed line arrows that were not displayed during the experiment.

accurately as possible until the end of the trial, signalled by the disappearance of the two segments aside the gauge. At the trial offset, subjects were instructed to terminate the contraction and completely relax their hand for the duration of the inter-stimulus interval lasting either 5, 7 or 9 s. The choice of task durations were motivated by ensuring a stable and reliable contraction period; secondly that we recorded a sufficient number of trials, for both 10% and 30% conditions, to allow meaningful correlations between fMRI responses and single-trial performance to be calculated, without creating an over-long total experimental duration. Isometric contractions at both force levels were executed in two experimental conditions (see Fig. 1 for a schematic representation of the task display):

1) Visuomotor condition (VM), where a horizontal, black force indicator bar appeared centrally in the force gauge upon trial onset. The vertical position of this horizontal indicator provided continuous visual feedback information to the subject about the exerted contraction force (Fig. 1B & C). The force indicator was removed from the visual display at trial offset.
2) Motor condition (M), where subjects were asked to perform the isometric contraction without the display of the horizontal force indicator (Fig. 1D & E).

Although matching the target force level was obviously more difficult in this M-task, subjects had been familiarised with the task during a single-run of each of the tasks conducted outside of the MRI scanner immediately before the fMRI experiment and were reasonably competent at achieving two different force levels. As discussed below, we considered the maintenance of a stable force level to be the most important constituent of good task performance, instead of the difference between the applied contraction force and the target level. Experimental cues were visually presented to participants via a projector display and the visual display was controlled using the Psychophysical toolbox (Brainard, 1997) running in Matlab (Mathworks). Immediately before fMRI scanning each subject performed a practice run of the VM and M tasks to familiarize them with the task and eliminate learning effects.

During fMRI, two experimental runs of each of the VM- and M-task conditions were acquired in an interleaved order that was randomised across subjects. Each run consisted of thirty 10% and thirty 30% trials presented in a pseudo-random order. Within the same scanning session, following the first two contraction runs, a six-minute resting-state scan was also acquired, during which subjects were instructed to lie still, keep their eyes open and think of nothing in particular. This run served to minimize the muscular fatigue effects during the tasks.

Quantification of single-trial behavioural performance

Separately for M- and VM-tasks, single-trial force time courses were normalized to each individual subjects' MVC to enable comparison between individuals. Single-trial force time courses were then used to quantify subject's behavioural performance in the two tasks. In this study, we conceptualise better performance as trials where contraction force is maintained closer to the target level for the maximum time, with the minimum variation (error). Accordingly, we defined a metric to quantify single-trial performance. We did not analyse the first 400 ms of each trial as the data in this initial period encompassed the subject's reaction time and was not informative about the stability of the contraction. We also excluded the final 300ms so that the effects of trial offsets were not included.

For each single trial T, and time point x, we calculate the absolute value of the error in the contraction force f as:

$$\Delta F(T, x) = |(f(T, x) - Q(T))| \quad (1)$$

For the VM-task, *Q(T)* was defined as the target force, either 10% or 30% of subject's MVC. For the M-task, *Q(T)* was defined in each trial as force attained in that trial (the average force in the final two seconds of the trial), as we were primarily interested in quantifying the stability of the sustained contraction rather than the precision in reaching the remembered target. By adopting this strategy we avoid adversely penalising trials where stable contractions were made at a different force from the target level. Therefore for the M-task, *Q(T)* was defined as:

$$Q(T) = \frac{\int_{2.7}^{4.7} f(T, x)}{2} \quad (2)$$

For both VM and M-tasks, we quantified the performance either in executing the whole task (WT, including reacting to the go signal, attainting, and maintaining the required force) or in the ability to maintain a stable contraction (SC). To do this, two temporal windows were used, and the above parameter was estimated either on the whole trial (0.4–4.7 s) or on the stable contraction period only (T_{FI1} – 4.7 s), with T_{FI1} defined as the first intersection between the contraction force (f) and Q. T_{FI1} represented the end of the initial phase of rapid increase in contraction force and the beginning of the phase where subjects attempted to maintain a sustained force level using only smaller adjustments in contraction (see Fig. S1). T_{FI1} was chosen in this way as it allowed accurate single-trial quantification of the contraction duration and avoided inaccuracies inherent when using values derived from average force time courses or arbitrarily chosen time intervals.

As introduced in seminal studies investigating the role of noise in the motor system control (Harris and Wolpert, 1998), we used the coefficient of variation of the exerted pressure as a performance index. In fact, physiological observations show that the neural control signals are corrupted by noise whose variance increases with the size of the control signal (Brashers-Krug et al., 1996; Shadmehr and Mussa-Ivaldi, 1994). In particular isometric contractions of the hand muscles exhibit variability in force production that is proportional to the mean force exerted (Jones et al., 2002), with the variability in continuous isometric force production thought to arise from the statistical variability and synchrony in the discharge of motorneurons supplying the muscle (Kargo and Nitz, 2004).

The mean (μΔF) and standard deviation (σΔF) of ΔF were calculated and the final performance metric (P) was defined for each trial such that the variability of the error in the contraction normalised by the mean contraction force error:

$$P = \frac{\sigma \Delta F}{\mu \Delta F} \quad (3)$$

Consequently, larger values of P represented better trial performance in the form of a trial where the target force was matched more closely and with smaller variability for a longer temporal period.

To visualise the relationship between P_{WT}, P_{SC} and behaviour and to check the effectiveness of the single-trial parameterisation to differentiate trials with “good” performance from those with “bad” performance, trials were sorted by values of P_{WT} and P_{SC}. The single trial force timecourses of each subject were sorted into lower and upper 25% quartiles, separately for P_{WT} and P_{SC}. These quartiles were then averaged across the group. For each experimental run timecourses of single-trial P_{WT} and P_{SC} values were used to create zero-mean parametric modulators of task performance for use in subsequent fMRI general linear model (GLM) analysis. Finally, contraction force timecourses were averaged across trials for each subject and the mean force level during the stable contraction period (T_{FI1}- 4.7 s) was calculated separately for 10% and 30% trials and both VM- and M-tasks.

fMRI data acquisition

All experiments were conducted at the Birmingham University Imaging Centre using a 3T Philips Achieva MRI scanner. An eight channel phased-array head coil was used to acquire T1-weighted anatomical image (1 mm isotropic voxels) and four task-related whole-brain T2*-weighted, functional EPI data (365 volumes, 3x3×4 mm voxels, 32 slices, TR=2000 ms, TE=35 ms, SENSE factor=2, flip angle=80°). Cardiac and respiratory cycles were continuously recorded (pulse oximeter and respiratory belt). Electromyogram (EMG) was recorded during fMRI from the pollicis brevis muscle of the right thumb using a BrainVision EXG Amplifier. However, due to difficulties in removing MR gradient artefacts induced by fMRI these data are not considered further here.

fMRI data preprocessing

All fMRI analyses were carried out using FSL 4.1.8 (www.fmrib.ox.ac.uk/fsl). Prior to statistical analysis automated brain extraction using BET and motion correction using MCFLIRT (Jenkinson et al., 2002) were applied. We calculated the mean of the relative head movement parameter over the 3 TRs (6 s) immediately following each stimulus delivery (the contraction duration) in every run. The group mean movement across all trials for each condition was: Feedback 10%=0.08 mm ± 0.03; Feedback 30%=0.07 mm ± 0.02; No Feedback 10%=0.07 mm ± 0.02; No Feedback 30%=0.08 mm ± 0.02. No significant differences in movement between conditions were observed and we therefore conclude our fMRI responses are not confounded by head motion. Physiological noise correction was then performed using custom Matlab code based on the RETROICOR routine (Glover et al., 2000). Subsequently, slice-timing correction, spatial smoothing (5 mm FWHM Gaussian kernel), high-pass temporal filtering (100 s cut-off) and registration to high-resolution anatomical and MNI standard brain images was performed.

To further control for potential differences in heart-rate and depth of respiration between trials and between experimental conditions the respiration-per-volume-time (RVT) (Birn et al., 2008) and the variation in the heart-rate interval (HRI) (Chang et al., 2009; de Munck et al., 2008) were computed from the physiological data for all experimental runs. These data were downsampled to form continuous time-courses with one sample point per TR interval and convolved with the respiration-response function (Birn et al., 2008) and cardiac-response function (Chang et al., 2009) respectively to form confound-of-no-interest regressors for GLM analysis. Modelling these physiological fluctuations in the GLM allows us to account for BOLD signal variability that is unrelated to the neuronal response to the task. This improves our ability to reliably interpret trial-by-trial correlations between variability in task performance and BOLD response amplitude as reflecting shared neuronal origins, rather than physiological origins. Furthermore it aids our comparison of the BOLD response amplitude between task conditions, by removing the potential confound of alterations in cardiac or respiratory rate that may accompany changes in the difficulty or cognitive demand of task (Birn et al., 2009).

fMRI data analysis

GLM analyses were independently performed for VM- and M-task data, separately incorporating single-trial values of either P_{WT} or P_{SC}. The construction of the design matrix followed the same procedure in each instance. First-level design matrices were constructed for each run using twelve regressors: 1) the main effect of 10% contraction trials; 2) the main effect of 30% contraction trials; 3) the parametric modulation of single trial P for 10% trials; 4) the parametric modulation of single trial P for 30% trials; 5) RVT; 6) HRI; 7–12) the six motion parameters of head translation and rotation were incorporated as confounds of no interest. Regressors 1 & 2 were modelled by square wave functions of the stimulus timings with consistent, non-zero amplitude during the contraction periods, whereas regressors 3 & 4 were amplitude modulated during the contraction periods according to the single-trial variability in either P_{WT} or P_{SC}.

Regressors 1–4 were convolved with the canonical double-gamma haemodynamic response function and first-level statistical analyses were performed using FEAT 5.98. Positive and negative contrasts were set on all regressors. Separately for 10% and 30% contractions, first-level results were combined across both runs, to calculate an average response per subject at the second-level with fixed effects, and then combined across all subjects at the third-level using FLAME 1 mixed effects (Woolrich et al., 2004). All Z-statistic images were thresholded

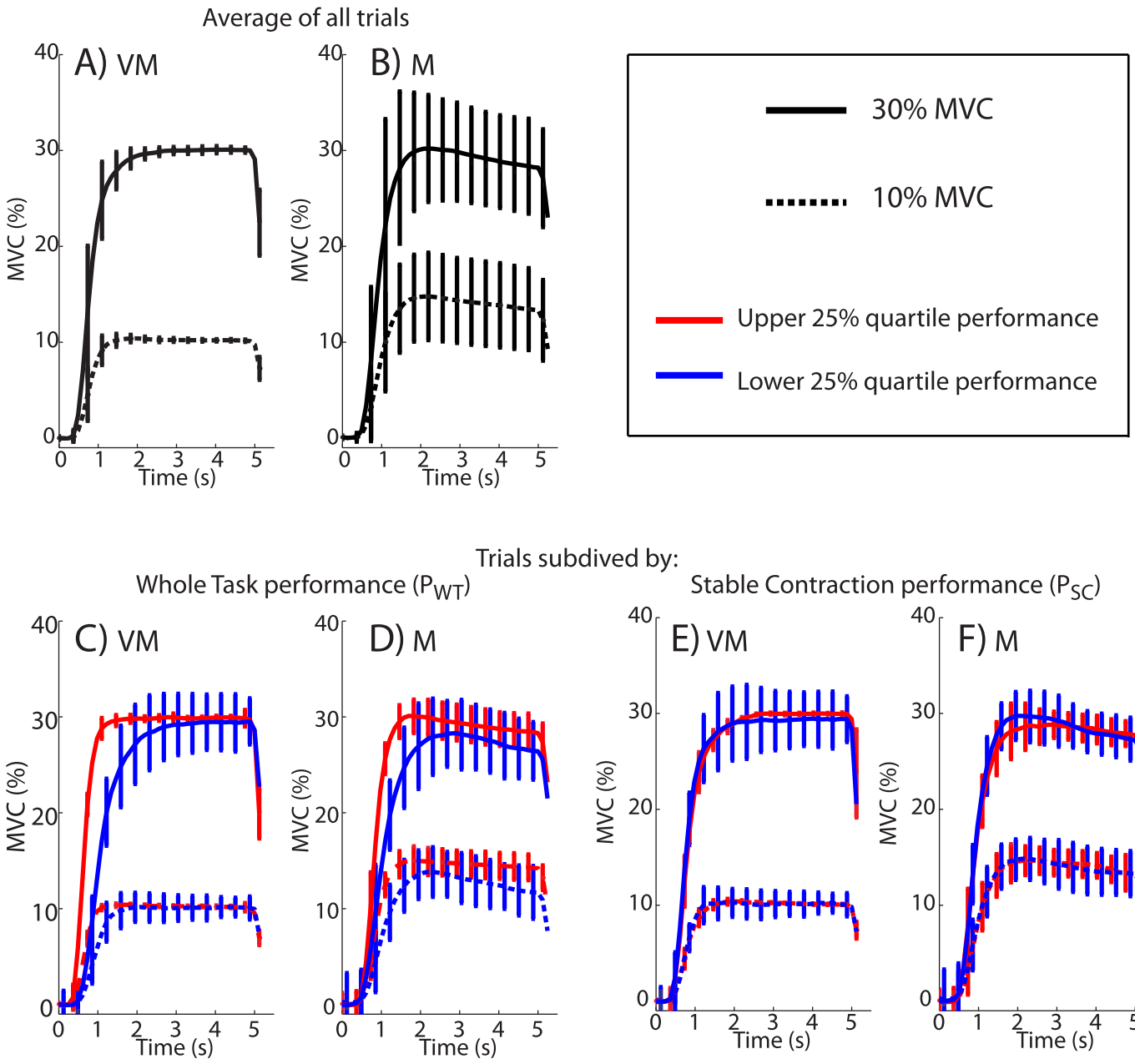

Fig. 2. Group average behavioural performance. Contraction force time courses averaged across all subject's data in the VM-task (A) and M-task (B). To illustrate the distinction between good and poor task performance that was provided by single-trial response metrics, trials were separately sorted into upper and lower quartiles of P_{WT} (C,D) and P_{SC} (E,F). The group average of the lower (blue) and upper (red) quartiles are plotted for the VM-task (C,E) and the M-task (D,E) respectively. In all plots, 10% and 30% trials are plotted in dashed and solid lines respectively. Error bars represent the standard deviation across subjects. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

using clusters determined by a $Z > 3.1$ and cluster corrected significance threshold of $p < 0.05$. Further third-level contrasts were used to: 1) compare the average BOLD responses between the main effects of VM- and M-tasks; 2) calculate the average BOLD response to both 10% and 30% contractions; 3) calculate the difference in the BOLD response between the 10% and 30% contractions; 4) calculate whether the correlation between the BOLD response and each of the P_{WT} and P_{SC} single-trial performance measures was different between 10% and 30% contractions.

Results

Behaviour

All subjects successfully performed both VM and M isometric contraction tasks. The group average behavioural performance data for the VM- and M-tasks is plotted in Fig. 2A and B respectively. Responses to both tasks featured an approximately 400ms reaction time delay before the contraction force increased significantly from pre-stimulus baseline levels. Contraction force increased rapidly until a period of stable contraction was reached which was then maintained until trial offset. The parameter T_{FI1}, defined as the first intersection of the contraction force with the target force, was measured in the group average as VM-task: 10%=1.5 ± 0.2 s; 30%=1.7 ± 0.3; M-task: 10% =1.4 ± 0.4 s; 30%=1.3 ± 0.2. The latency of T_{FI1} was significantly longer in the VM-task than in the M-task for the 10% contractions (in 9/17 subjects) and 30% contraction (14/17 subjects) trials ($p < 0.05$, students's t-test).

The accuracy in matching the 10% and 30% target-force level in the visual feedback task (A) is in contrast to the tendency for subjects to

respectively over/underestimate the force during the 10% and 30% trials in the M-task. At the group-level we observed a significant difference in subject's mean stable contraction force (T_{FI1}- 4.7 s) between the 10% and 30% contraction trials in both the VM- and M-tasks (both $p < 0.001$, paired t-test). Much greater within- and between subject variability in the stable contraction force was observed during the M-task, reflecting the greater uncertainty in performance in the absence of visual feedback, but all subjects performed a consistent contraction with a clear distinction between 10% and 30% conditions. No significant difference in subject's mean stable contraction force was observed between VM- and M-tasks for either 10% (p=0.82) or 30% trials (p=0.62, paired t-tests), indicating that the contraction force was comparable with and without feedback. MVC was consistent across subjects, group mean ± standard deviation=9.7 ± 1.4 kg; range=7.25–12 kg. No linear correlation was observed between subject's MVC and mean performance measure (P_{WT}) across trials for any condition: 10% VM (R=0.31, p=0.21); 30% VM (R=0.08, p=0.70); 10% M (R=0.19, p=0.47); 30% M (R=0.21, p=0.42). Furthermore, no correlation was observed between MVC and mean maximum contraction force for either 10% (R=−0.04, p=0.88) or 30% trials (R=−0.25, p=0.32) indicating that subject's MVC did not determine their performance. In the M-task we observed a trend for a small, steady decrease in contraction force towards the end of the trial (Fig. 2B), suggesting that subjects were not able to sustain the contraction as consistently as in the VM-task.

The group average of trials sorted into lower and upper quartiles of P_{WT} for 10% and 30% contractions are displayed in Fig. 2C (VM-task) and 2D (M-task) tasks. Individual subject data of upper and lower P_{WT} quartiles can be seen in Fig. S2, clearly showing that shows that our metric enables good performance to be distinguished from bad performance for every subject. Larger values of P_{WT} (red curves) were associated with better trial performance than seen in trials with low values of P_{WT} (blue curves). In particular, good performance could be qualitatively identified by: faster response time, matching of the contraction force to the target force with less error and therefore greater accuracy and stability, and longer duration maintenance of steady contraction. See Fig. S3 for a comparison of single-trial force timecourses with their corresponding values of P_{WT}, μΔF, and σΔF. We observed that: a) the highest P_{WT} values occurred when the mean difference between contraction and target force level (μΔF) was relatively small b) between trial variability of μΔF was larger than that of σΔF; c) there was a larger difference in μΔF between good and bad performance trials than there was in σΔF. Therefore we conclude that it is primarily μΔF that determines the value of our metric P_{WT} in this task. μΔF was much larger in the bad than the good trials, whereas σΔF only varied a little between good and bad trials.

In the VM-task, lower and upper quartiles of P_{WT} displayed equivalent contraction force levels during the stable period (approximately 2–5 s), indicating that subjects consistently attained the target force matching. Behavioural performance varied in the speed and accuracy with which the target force was attained.

However, differences in the mean force level during the stable period of contraction were observed between upper and lower quartiles of P_{WT} in the M-task. Here, upper quartile trials of P_{WT} (better performance) again displayed faster response times, longer periods of steady contraction maintenance and smaller errors compared to lower quartile trials (Fig. 2D). However, the error in the contraction maintenance during the upper quartiles was considerably larger than observed in the VM-task.

Fig. 2E and F displays the group average of trials sorted into lower and upper quartiles of P_{SC} for 10% and 30% contractions and for VM and M-tasks respectively. In contrast to P_{WT}, P_{SC} differentiated between trial performances only in the variability in the maintenance of the contraction. No difference in either the response time, the average contraction force, or the length of time for which the steady contraction was maintained was observed between lower and upper quartiles of P_{SC} for either the VM- or the M-tasks. Therefore comparing BOLD response correlates of P_{SC} with P_{WT} will enable the dissociation between the brain mechanisms associated with greater response speed to match the target and the accuracy to which the contraction was maintained.

fMRI

BOLD responses to the main effect of isometric contractions

Significant BOLD responses were observed to both VM and M-tasks across the subject group. The main effect of isometric contractions (grouped across both 10% and 30% trials) showed BOLD signal increases during the task, compared to resting fixation, in widespread brain regions (Figs. 3 and 4, see Fig. S4 for statistical maps of individual conditions). VM and M-tasks showed significant BOLD responses in the brainstem, cerebellum, bilateral thalamus, basal ganglia, bilateral insula, anterior cingulate cortex (ACC), bilateral inferior and superior visual cortex, bilateral inferior frontal gyrus (IFG), middle frontal gyrus (MFG), prefrontal cortex (PFC), contralateral primary motor cortex (M1), bilateral secondary sensorimotor cortex (S2), bilateral dorsal and ventral premotor cortex (PMd, PMv), bilateral posterior parietal cortex (PP) and the supplementary motor area (SMA), similar to previous reports (Castiello, 2005; Cramer et al., 2002; Debaere et al., 2003; Dettmers et al., 1995; Ehrsson et al., 2000; Keisker et al., 2010; Kuhtz-Buschbeck et al., 2001; Ogawa et al., 2006; Vaillancourt et al., 2003). In the VM-task only, a significant decrease in BOLD signal (negative BOLD response, NBR) was observed in primary visual cortex V1, ipsilateral M1, ipsilateral prefrontal cortex and midline prefrontal cortex (Fig. 4).

Modelling variations in the depth of subject's breathing (RVT) and HRI as confounds of no interest in the GLM showed that BOLD responses (Fig. S5) were significantly correlated with these physiological fluctuations in widespread areas of grey matter that also responded significantly to the task, in agreement with previous studies (Birn et al., 2008; Chang et al., 2009). Controlling for both cardiac and respiratory physiological variability in this manner, as well as for stimulus-locked motion, provides confidence that these factors do not confound our fMRI measurements of brain activity.

Differences in BOLD response to contractions between experimental conditions

Significant differences in the BOLD responses to isometric contractions were observed between 10% and 30% force levels and also between VM and M-tasks (Fig. 3). Fig. 3A displays the regions where the BOLD response to 30% contractions was significantly larger than the response to 10% contractions. In both the M- (blue) and the VM- (red) tasks, the BOLD response amplitude was observed to increase with increasing contraction force in the brainstem, cerebellum, thalamus, basal ganglia, primary visual cortex and bilateral primary motor cortex (Fig. 3A). In addition, the BOLD response to 30% contraction trials was more pronounced than the response to 10% trials (Fig. 3A, more red-yellow than blue) in thalamus, basal ganglia, bilateral S1/M1, bilateral S2, SMA, lateral visual cortex, precuneus and midline and bilateral frontal cortex. Interestingly, very little significant difference in the BOLD response between the VM- and M-tasks was found in the contralateral M1 region that showed the primary response to contractions, reflecting that the basic motor output was comparable between tasks.

The primary motor cortex, basal ganglia and cerebellar regions which we observed to exhibit a significantly larger BOLD response to the main effect of 30% than 10% trials (Fig. 3A) are consistent with previous reports that these areas encode greater motor output (Cramer et al., 2002; Dettmers et al., 1995; Ehrsson et al., 2001; Keisker et al., 2009; Kuhtz-Buschbeck et al., 2008). The difference in the BOLD response amplitude between the main effect of 10% and 30% trials was found to be greater during the VM than during the M-task, both in

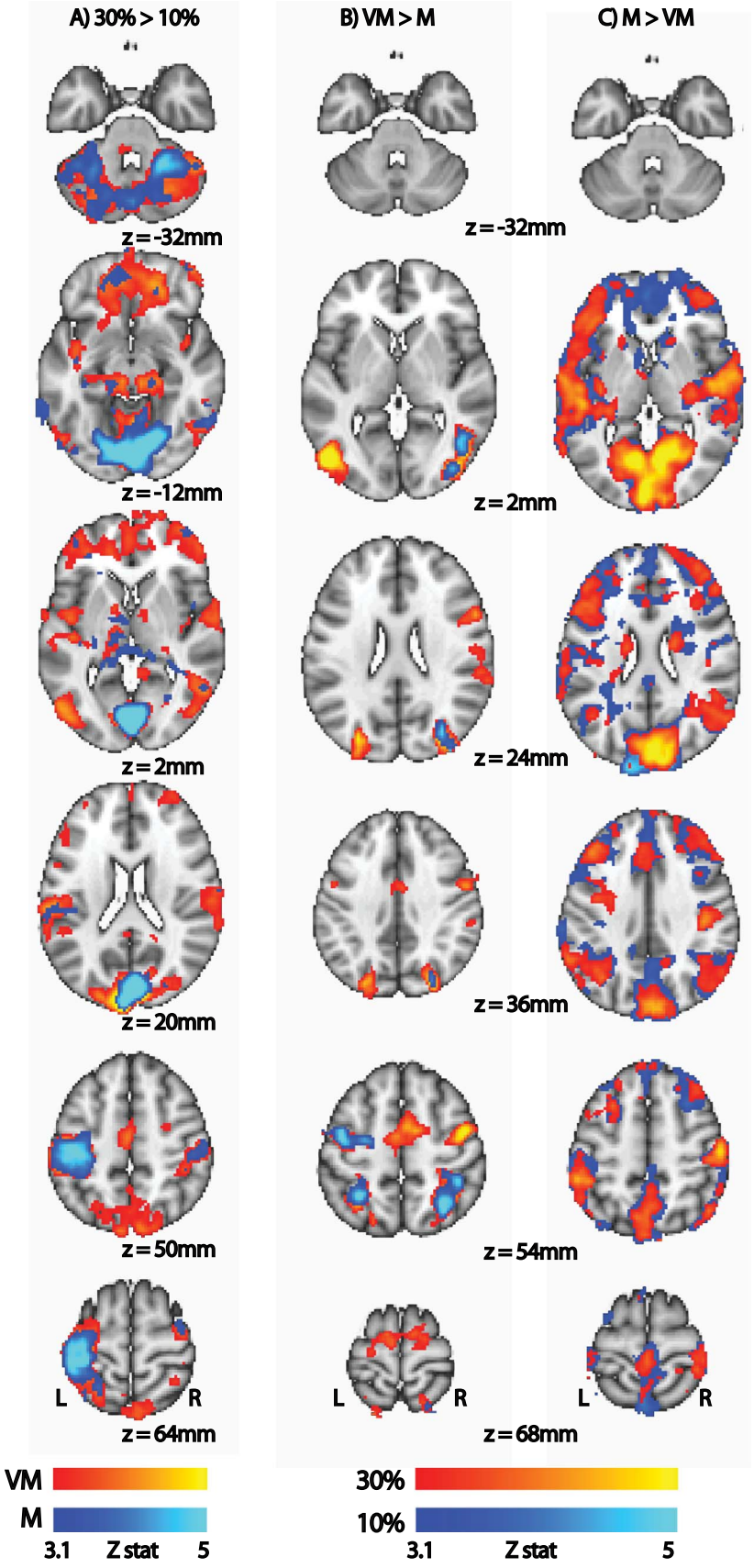

Fig. 3. BOLD responses dependent upon the mean effect of handgrip force (10% vs. 30% MVC) and VM vs. M conditions. Statistical maps displaying brain regions where the BOLD response was significantly larger: A) to 30% than 10% contractions; B) to VM- than M-task contractions; C) to M- than VM-task contractions. No brain region displayed stronger BOLD responses to 10% than 30% contractions on average. In A) the group mean BOLD responses to the M-task (blue) are displayed superimposed upon group responses to the VM-task (red-yellow). The group mean BOLD responses to 10% contractions (blue) are shown superimposed upon (B) and beneath (C) the group responses to 30% contractions (red-yellow). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

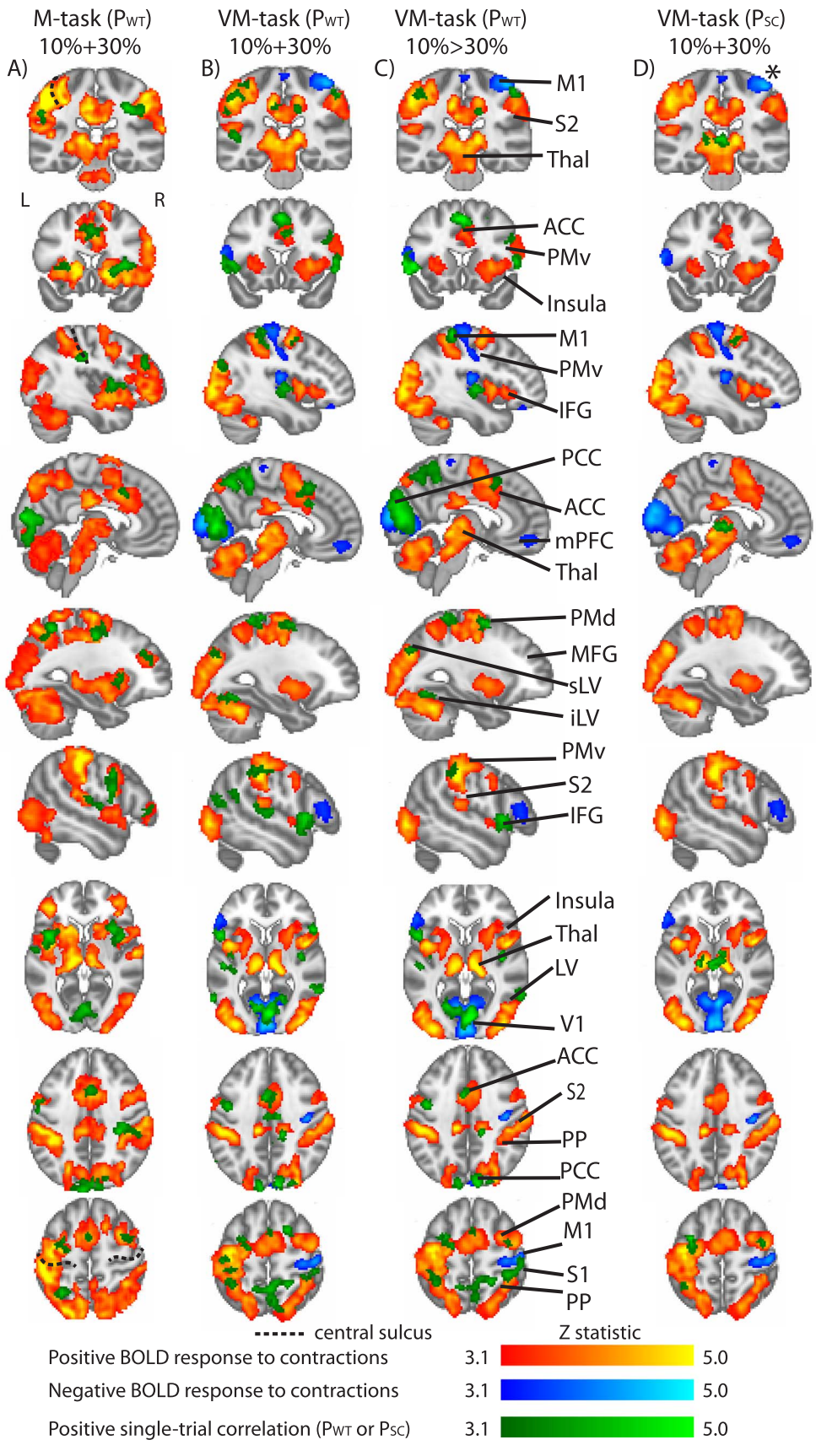
M-task (PWT)
10%+30%
VM-task (PWT)
10%+30%
VM-task (PWT)
10%>30%
VM-task (PSC)
10%+30%
A)
B)
C)
D)
L
R
M1
S2
Thal
ACC
PMv
Insula
M1
PMv
IFG
PCC
ACC
mPFC
Thal
PMd
MFG
sLV
iLV
PMv
S2
IFG
Insula
Thal
LV
V1
ACC
S2
PP
PCC
PMd
M1
S1
PP
central sulcus
Z statistic
Positive BOLD response to contractions
3.1
5.0
Negative BOLD response to contractions
3.1
5.0
Positive single-trial correlation (PWT or PSC)
3.1
5.0

Fig. 4. Mean BOLD responses to VM and M-tasks and single-trial responses correlated with task performance. Group BOLD response to M (A) and VM-task (B) isometric contractions and VM-task BOLD correlations with single-trial P_{WT} (A,B,C) and P_{SC} (D) performance. C) shows the brain regions where the single-trial BOLD-P_{WT} correlation was stronger for 10% than 30% contraction trials in the VM-task. D) shows the single-trial correlations between the BOLD response and P_{SC} grouped across both 10% and 30% conditions. The brain regions that exhibit positive trial-by-trial correlations (green) are shown superimposed upon the brain regions that exhibited positive (red-yellow) and negative (blue) mean BOLD responses to both 10% and 30% trials for the respective task. Brain slices are shown for (from top to bottom) y=−28, 16 mm; x=40, 6, −30, −52 mm; z=4, 38, 60 mm. * marks the location of the negative BOLD response in ipsilateral M1. The dashed line marks the central sulcus. Thalamus (Thal), anterior and posterior cingulate cortex (ACC, PCC), inferior (i) and superior (s) lateral visual cortex (LV), primary visual cortex (V1), inferior frontal gyrus (IFG), middle frontal gyrus (MFG), lateral and medial prefrontal cortex (lPFC, mPFC), primary motor cortex (M1), primary and secondary somatosensory cortex (S1, S2), dorsal premotor cortex (PMd), posterior parietal cortex (PP). All maps were thresholded using clusters determined by a $Z > 3.1$ and cluster corrected significance threshold of $p < 0.05$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

terms of the statistical significance and spatial extent of the activations. This result is consistent with the observation that the difference in mean contraction force between 10% and 30% trials was larger during the VM-task than during the M-task (Figs. 2A & 2B). Although containing similar motor contraction components, the difference in visual feedback created an intrinsic difference in task difficulty and sensory stimulation between the VM and M-tasks. Therefore differences in brain activity observed between tasks reflect a combination of these factors and isolating the individual contributions of these effects is not possible without further study.

Figs. 3B and 3C allow comparison of the activation patterns between the M- and VM-tasks for the two contraction levels. Larger amplitude BOLD responses were observed during the VM-task bilaterally in lateral visual cortex, premotor cortex, parietal cortex and the SMA (Fig. 3B). The spatial extent and degree of bilaterality of these activations was greater for the 30% (red) than for the 10% (blue) trials. The reverse contrast revealed larger amplitude BOLD responses during the M- than VM-task in primary visual and auditory cortex, precuneus, dorsal ACC, bilateral supramarginal gyrus, bilateral intra-parietal lobe (IPL) and bilateral prefrontal cortex (Fig. 3C). While the regions themselves were very similar for 10% and 30% contractions, the spatial extent of the regions showing larger BOLD responses during the M-task was greater for the 10% than for the 30% contractions. The observation of significantly larger BOLD responses in primary visual cortex during the M-task compared to the VM-task arises because primary visual cortex was deactivated by the VM-task but not by the M-task.

Trial-by-trial correlations between the BOLD response and task performance (P_{WT})

In both VM and M-tasks, we observed significant positive correlations between single-trial P_{WT} and the amplitude of the BOLD response when grouped across both 10% and 30% trials (Fig. 4, green). These correlations indicate that these brain regions exhibited larger BOLD responses during trials with better task performance. Correlations between P_{WT} and the BOLD response during the M-task were observed bilaterally in V1, insula, posterior parietal cortex, frontal cortex and premotor cortex as well as the ACC (Fig. 4A). Correlations between P_{WT} and the BOLD response to the VM-task were observed bilaterally in inferior and superior lateral visual cortex, V1, IFG, posterior parietal cortex (Brodmann areas BA5 and BA7), PMv, S1 and M1 as well as the precuneus and ACC (Fig. 4B). Common regions of BOLD-P_{WT} correlation across both VM- and M-tasks were bilateral PMd, IFG, posterior parietal cortex, V1, S2 and the ACC. In all these areas correlations were more significant in the VM-task. Correlations that occurred only in the M-task were observed in bilateral insula and bilateral prefrontal cortex.

Further analysis showed significant differences in the BOLD-P_{WT} correlation between the 10% and 30% contractions of the VM-task (Fig. 4C). The BOLD-P_{WT} correlation was significantly stronger for the 10% than the 30% contraction trials in lateral visual cortex, ACC, bilateral IFG, bilateral PP, premotor cortex, S1 and M1 suggesting that greater activity in these regions was most important for good contraction performance. No significant difference in the BOLD-P_{WT} correlation was observed between the 10% and 30% contractions for the M-task.

These statistical maps of significant BOLD-P_{WT} correlation link variations in behaviour to variations in brain responses and illustrate the brain regions that are most important for the best task performance. However, in the VM-task, better performance in the upper quartile trials of P_{WT} was associated with faster response times and longer duration of force target matching, in addition to lower contraction errors (see Fig. 2C & D). Therefore it is not possible to relate the strength of BOLD-P_{WT} correlation which we observe to any single one of these factors. To enable better dissociation in these effects we also quantified P_{SC} which differentiates trials only in terms of the force error during the stable contraction period. By focussing on the stable contraction period, P_{SC} has the further advantage of removing contributions of overshoots in the force response to calculation of P which can lead to penalisation of these trials compared to those where contraction approaches the target force steadily.

Trial-by-trial correlations between the BOLD response and P_{SC}

We observed significant positive correlations between single-trial P_{SC} and the amplitude of the BOLD response grouped across both 10% and 30% trials for the VM-task (Fig. 4D). BOLD-P_{SC} correlations were observed in bilateral thalamus, PP and PMd (Fig. 4D), suggesting that greater activity in these regions was most important in supporting the precise control of visuo-motor contractions with lowest errors. No significant difference in BOLD-P_{SC} correlations was observed between 10% and 30% trials in either task. Furthermore, no significant correlation was observed between P_{SC} and the BOLD response to the M-task.

Discussion

In this study we combined BOLD fMRI measurements with single-trial metrics of behavioural performance to identify the brain regions relevant for the fine control of isometric hand contractions both with and without visual feedback. Selective performance indices enabled us to isolate the brain regions responsible for accurately maintaining a stable isometric contraction from those supporting execution of the whole task, which includes the response to the go and stop signals, increasing contraction to reach the target force level followed by small force adjustments to maintain the target level.

We found that modulations in the activity of a bilateral fronto-parietal, visuo-motor network correlated significantly with task-performance. Larger amplitude BOLD responses were observed in trials where subjects performed more accurate matching of the target force. The positive trial-by-trial correlation between behavioural performance and BOLD signal in this network was more significant in the following circumstances: 1) when visual feedback of task force was provided compared to without feedback (Fig. 4A & B); 2) when performing 10% compared to 30% MVC visual feedback trials (Fig. 4C); 3) when performance was quantified based upon the whole trial rather than just the stable period of contraction (Fig. 4D). In general we observed that the majority of the BOLD responses to the main effect of the VM- and M-tasks either scaled with contraction force strength and/or were modulated by the presence/absence of visual feedback (see SI for further discussion). Single-trial BOLD responses to the VM-task were found to exhibit the strongest coupling with behaviour whereas the M-task activation displayed widespread brain activity that was weakly correlated with performance suggesting it was poorly efficacious as well

as fatiguing as demonstrated by a small loss of force at the end of M-task trials.

These data show widespread brain deactivations during the VM-task. NBR in ipsilateral S1/M1 have previously been reported during unilateral sensorimotor tasks and are thought to represent a decrease in local cerebral blood flow, oxygen metabolism and neuronal activity reflecting cortical inhibition of the unstimulated hand to help improve task performance (Allison et al., 2000; Liu et al., 2011; Mullinger et al., 2014; Schafer et al., 2012; Stefanovic et al., 2004). Deactivation of V1 during the VM-task is more unexpected and could potentially arise from strong attention to the motion of the force indicator prioritising activation of the lateral visual regions over those of V1, which creates an apparent deactivation of the primary visual region. We observed that the deactivation of V1 was stronger in the VM 10% than the VM 30% condition (Fig. S4) which is consistent with previous reports of increased deactivation occurring with increased task difficulty (Hairston et al., 2008; McKiernan et al., 2003). This effect could be conceptualised as resulting from within-network competition of processing resources, analogous to cross-modal suppression of auditory cortex when attending to visual information (Laurienti et al., 2002; Mozolic et al., 2008). Alternatively, as we did not record eye-movements we cannot rule out the possibility that differences in eye-movements between conditions drive different modulations of visual cortex BOLD signal (Bristow et al., 2005; Freitag et al., 1998; Tse et al., 2010) such are observed between the VM and M-tasks.

Single-trial performance quantification allows dissociation between components of network activity recruited by isometric contraction

We made additional and complementary observations by isolating the brain structures relevant for the control of the stable isometric contractions from those relevant for the execution of the whole task. We found that the BOLD response in widespread areas of the visuo-motor network correlated with P_{WT}. However, from this result alone we were unable to interpret which of three factors of performance quality (Fig. 2C, response time; contraction time or force error) was driving the correlation with fMRI measures of brain activity. Consequently, we further quantified performance only during the period of stable contraction (P_{SC}) in order to differentiate the effect of force error from the response time and length of the contraction (Figs. 2E, 2F).

We found that bilateral thalamus, caudate, M1 and premotor cortex (Fig. 4D) are the most important for maintaining an accurate, stable isometric contraction during the VM-task. In comparison, bilateral inferior and superior lateral visual cortex, V1, posterior parietal cortex, M1, S1, S2, premotor cortex, the IFG and MFG as well as the precuneus and ACC were most involved in determining the response time and the duration of contraction over the whole-trial period in the VM-task (Fig. 4B). In the absence of visual feedback, single trial BOLD-P_{WT} correlations suggest that only activity in bilateral V1, insula, parietal cortex, prefrontal cortex, premotor cortex and the ACC was associated with task performance over the whole-trial period (Fig. 4A). Furthermore, we observed no BOLD responses during the M-task that were associated specifically with trial-by-trial variability in the maintenance of the stable contraction (P_{SC}).

These results reflect that the M-task comprised a less precise and controlled action, without the regular adjustments of contraction force that were required in the VM-task. M-task performance required subjects to increase contraction force until an internally chosen level was reached. Evidently, maintaining this contraction force using only somatosensory feedback did not require the repeated, small corrective adjustments that were an important feature for good performance of the VM-task. In fact, a small but steady decline in force was observed during the stable contraction period (Fig. 2B). As indicated by the larger error-bars on Fig. 2B compared to Fig. 2A, the variability in the M-task behaviour was much larger than that of the VM-task, however the results of the BOLD-behaviour analysis suggest that this increased variability does not reflect greater information content. Therefore we suggest that the cortical response to the M-task, which in frontal and parietal areas (Fig. 3C) was more widespread than observed to the VM-task, were less functionally effective and involved recruitment of neuronal resources which did not succeed in compensating behavior to the level observed with visual feedback, and in fact could lead to fatigue.

One of the largest spatial differences in single-trial BOLD-P_{WT} correlations between tasks were the activations in the IFG and bilateral parietal regions only seen during the VM-task, which reflects the integration of visual and somatosensory information to aid task performance. This finding is supported by both human and primate studies demonstrating that the parietal cortex and its projections to the dorsal and ventral premotor cortex are fundamental to visuomotor processing (Calton et al., 2002; Desmurget et al., 1999; Ellermann et al., 1998; Goodale and Milner, 1992; Hamzei et al., 2002; Jeannerod et al., 1995; Tanne-Gariepy et al., 2002) and particularly in the reactive control of fine-tuned precision grip tasks (Dafotakis et al., 2008; Davare et al., 2007; Ehrsson et al., 2001; Haller et al., 2009). The co-operation of these areas in transforming visual information into action occurs via the strong connections between them which form parallel parieto-premotor circuits (Rizzolatti et al., 1998; Wenderoth et al., 2006; Wise et al., 1997). The IPL in particular has been shown to help control movements by working as an interface between the perceptual and motor systems (Grefkes and Fink, 2005). The parietal cortex receives information via projections from lateral visual regions, where we also observe BOLD-behaviour correlations, which itself receives input from primary visual cortex (Boussaoud et al., 1990). Lateral visual regions extract the relevant spatiotemporal information of the feedback signal, whereas the parietal regions make the necessary sensory transformations for integrating it with the required hand movements.

The only brain areas that displayed a BOLD-P_{WT} correlation during the M-task but not the VM-task were the bilateral prefrontal and the insula cortex. Activation of prefrontal cortex was also more widespread bilaterally in the M-task (Fig. 3C), perhaps suggesting its recruitment mediated top-down cognitive control (Koechlin et al., 2003; Miller and Cohen, 2001) required to perform the contraction without feedback. BOLD responses to the main effect of contractions were comparable between VM and M-tasks in the insula cortex, therefore the correlation with behaviour perhaps reflects the importance of a greater engagement of internal processes during M-task performance in insula regions known to represent high-level functions such as saliency and attentional control (Menon and Uddin, 2010; Seeley et al., 2007).

Precise control of low force output requires greater neuronal recruitment but only during visual feedback

During the VM-task, BOLD-P_{WT} correlations were more significant during 10% than 30% trials (Fig. 4C) in bilateral premotor cortex, the IFG and posterior parietal areas, possibly reflecting the finer motor control required for good task performance at the lowest force level. Taken together with the lack of a difference in BOLD-P_{WT} correlation between force levels in the M-task, we interpret these results as indicating that greater differences in task execution, and the brain processes supporting it, occurred between the 10% and 30% force levels in the VM-task compared to the M-task. The VM-task required finer motor control, and greater coupling between brain activity and motor output, to accurately maintain the contraction target force, particularly during the 10% contractions as large adjustments were required to correct small contraction errors, relative to the target force, compared to the 30% trials. In comparison, during the M-task, this type of fine motor adjustment was not required after the memorised, internal force level was attained and therefore no difference in brain activity was observed between the force levels.

Thalamocortical involvement in the fine control of force maintenance

The BOLD-P_{SC} correlations during the VM-task comprised a small, specific subset of the brain regions which were also activated by the main effect of the task: bilateral PMd, posterior parietal cortex, thalamus and contralateral M1 (Fig. 4D). No BOLD-P_{SC} correlations were observed in the IFG, S1 or anterior parietal areas where activity correlated with P_{WT}. This result suggests that steady force production is enhanced by strong M1-thalamic coupling; and furthermore that a greater coherence of thalamo-cortical signals is most important during accurate maintenance of isometric contractions rather than during the initiation and termination of the action. Ventral, posterior and intralaminar nuclei with direct input from motor cortex are known to participate in motor control.

Behaviour-BOLD correlations in M1 reflect greater neuronal recruitment required for better task performance

The positive BOLD-behaviour correlation in contralateral M1 during the VM-task is consistent with previous work which showed that increased activity in M1 was associated with reduced force error and increased precision of motor function (Carey et al., 2006; Coombes et al., 2010; Jenmalm et al., 2006). Interestingly, we observed significant positive BOLD-P_{WT} correlations during the VM-task only, in ipsilateral M1, which exhibited a negative BOLD response to the main effect of the task. Therefore during trials with the best performance, the BOLD signal was increased bilaterally in M1. This result suggests that on a trial-by-trial level, inhibition of ipsilateral M1 was not required to aid motor performance but instead more bilateral, excitatory recruitment of M1 was associated with better performance. The increased bilaterality of M1 and PMd activations with increasing contraction force further suggest that greater network recruitment is functionally relevant (Fig. 3A & B) (Dai et al., 2001; Derosiere et al., 2013).

Movement control requires continuous and reciprocal exchange of information between the brain areas involved in the execution of the motor task and those representing proprioceptive sensory information (Scott, 2004; Terao et al., 1999). Proprioception and cutaneous feedback is the most important information, with the tonic input from the skin enveloping the muscle essential for energizing the corticospinal output toward that muscle (Brasil-Neto et al., 1993; Rossi et al., 1998). In particular, we previously quantified the continuous functional balance between primary sensory and primary motor areas devoted to hand control that was required to maintain good motor performance (Tecchio et al., 2008). The present findings highlight the relevance of within-system somatosensory feedback since the integration of visual information, despite requiring greater brain processing, results in a movement realized with higher efficiency and less fatigue, even for the simple, everyday task that was used in the current study.

In summary, integration of behavioural and fMRI measurements allowed us to distinguish between average brain responses to single-hand contractions at different force levels generated with and without visual feedback, and the brain regions whose activity is most related to trial-by-trial fluctuations in task performance. When visual feedback was provided, we observed a bilateral visuo-parietal-motor network where increases in activity and bilateral network coherence were strongly coupled to improved behavioural performance. Without feedback the task recruited widespread brain activity that was largely uncoupled from behavioural performance. By parameterising single-trial task performance and investigating its correlation with regional BOLD responses, we were able to identify the brain areas which were of primary importance during the distinct temporal phase of sustained motor control, compared to those activated during the entire contraction. This work shows that single-trial responses contain additional information about task performance, over and above mean responses, and that linking temporal fluctuations in behaviour to brain activity allows a more detailed understanding of variations in motor task performance.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neuroimage.2017.01.017.

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